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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/685,432	10/10/2000	Jay M. Short	DIVER1280-3	4977

7590 02/08/2005

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/685,432	SHORT ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-12,16,17,19,20 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-12, 16, 17, 19, 20 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection (e.g., see 11/1/04 Response). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/1/04 has been entered. Claims 1-13, 15-20 and 22-26 were pending. Applicants canceled 2, 13, 15, 18 and 26. In addition, Applicants amended claims 1, 10, 16 and 19. Therefore, claims 1, 3-12, 16, 17, 19, 20 and 22-25 are currently pending. An action on the merit follows.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. The Written Description Rejection under 35 U.S.C. 112, first paragraph is withdrawn in view of Applicant's amendments and/or arguments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 112, second paragraph

3. Claims 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. ***Claim 22*** recites, "the polynucleotide of interest encodes a small molecule" in lines 1-2. The term "small" is a relative term, which renders the claim indefinite and/or unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b).

Response

4. Applicant's arguments directed to the above 35 U.S.C. 112, second paragraph rejections were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or newly amended arguments.

Applicants argue, "the phrase 'small molecule' as used in Applicants' specification and claims does not refer specifically to the size of the molecule ... [the Examiner's use of the] dictionary definition ... is 'unreasonable' ... [because the term] is used as a term of art. Applicants submit that those of skill in the art would understand

'small' in the phrase 'small molecule' as belonging to a term of art that distinguishes, for example, between enzymatic chemical compounds, and enzymatic polypeptides" (e.g., 11/1/04 Response, page 9, first paragraph). Applicants further cite various passages in the specification in support of this contention (e.g., see 11/1/04 Response, page 9, second paragraph wherein page 43, lines 4-18; page 45, lines 4-9; page 76, lines 31-32 are recited).

This is not found persuasive for the following reasons:

The Examiner contends that words of a claim must be given their "plain meaning" unless they are clearly defined in the specification (e.g., see MPEP § 2111.01). Here, none of Applicants' recited passages provide a definition for "small molecule" (e.g., page 43, lines 4-18 only uses the term "small molecule backbone" in order to exemplify a preferred screening embodiment; page 45, lines 4-9 only uses the term "small molecule pathway" in order to exemplify a another preferred screening embodiment; page 76, lines 31-32 only states the term "small molecule" can include, for example, a "receptor", but does provide any other examples and/or guidance that would further limit and/or define the term) and, as a result, the plain meaning must control. In addition, the Courts have upheld the use of "dictionary definitions" to determine the plain meaning of a claimed term (e.g., see *Ferguson Beauregard /Logic Controls v. Mega Systems*, 350 F.3d 1327, 1338, 69 USPQ2d 1001, 1009 (Fed. Cir. 2003)) (Dictionary definitions were used to determine the ordinary and customary meaning of the words "normal" and "predetermine" to those skilled in the art.). Thus, the Examiner's use of a dictionary is not "unreasonable" as purported by Applicants.

In addition, the Examiner notes that Applicants have not set forth any literature references defining the term "small molecule" (e.g., see *Arthur A. Collins, Inc. v. N. Telecom, Ltd.*, 216 F.3d 1042, 1045 [55 USPQ2d 1143] (Fed. Cir. 2000)) ("When prior art that sheds light on the meaning of a term is cited by the patentee, it can have particular value as a guide to the proper construction of the term, because it may indicate not only the meaning of the term to persons skilled in the art, but also that the patentee intended to adopt that meaning."). Here, Applicants have failed to provide any prior art references that support their contention that "small molecule" does not apply to the size of a molecule and that it would, on the other hand, distinguish "... between enzymatic chemical compounds and enzymatic polypeptides." Thus, Applicants contention that "small molecule" is a "term of art" that "does not refer specifically to the size" and that can be used to distinguish between "enzymatic chemical compounds, and enzymatic polypeptides" is simply not supported by either the specification or prior art.

Finally, the Examiner notes that examples in the specification employing an alleged "term of art" that are merely "illustrative" in nature do not provide an adequate definition for said term (e.g., see *Unitherm Food Systems Inc. v. Swift-Eckrich Inc.*, 71 USPQ2d 1705 (CA FC 2004)) (wherein the Court held that the term "golden brown" as it relates to the color of cooked meat products should be given the broader "dictionary definition" because the "five illustrative examples" in the specification were merely "exemplary" in nature and did not exhaustively delineate the scope of the term). Here, Applicants recited passages merely use the term "small molecule" to delineate "exemplary" embodiments (e.g., use as ligand, backbone, or constituent in biological

pathway) and thus do not provide and adequate definition for the term in accordance with *Unitherm Food Systems Inc. v. Swift-Eckrich Inc.* as set forth above.

Accordingly, the 35 U.S.C. 112, second paragraph rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. 102

5. Claims 1, 3-10, 16, 17, 19, 20 and 22-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Thompson et al. (US Patent No. 5,824,485) (Filed **April 24, 1996**).

For ***claim 1***, Thompson et al. (see entire document) disclose a method for screening molecular diversity, which anticipates the claimed invention. For example, Thompson et al. disclose **(a)** obtaining a plurality of polynucleotides derived from a mixed population of organisms or more than one organism (e.g., see column 25, paragraph 2, "Either DNA or RNA may be used as starting genetic material for preparing such libraries which may include cDNA libraries, genomic DNA libraries, as well as mixed cDNA/genomic DNA libraries, DNA fragments derived from a plurality of donor organisms, e.g., organisms described in Section 5.1.1, are introduced into a pool of host organisms, such that each host organism in the pool contains a DNA fragment derived from one of the donor organisms"; see also column 12, lines 38-44, "Any organism can be a donor organism for the purpose of preparing a combinatorial gene expression library of the invention ... from environmental samples [i.e., a mixed population] either cultivable or uncultivable"; see also column 12, line 18).

Thompson et al. also disclose **(b)** normalizing the plurality of polynucleotides to allow equal representation of all polynucleotides in the mixed population of organisms (e.g., see Thompson et al., column 14, lines 46-60, "Since it is unlikely that all donor organisms in an environmental sample may be propagated at the same rate, if at all under laboratory conditions, some of the donor organisms may overgrow and lead to the loss or dilution of slow-growing organisms. Thus, it may be preferable to prepare nucleic acids directly from donor organisms in an environmental sample without prior culturing in the laboratory"; see also column 32, lines 14-16, "all the positive clones can be pooled and used for making the biased [i.e., normalized] combinatorial gene expression library. The initial library [i.e., the library prepared directly from donor organisms] may be amplified so that DNA donor organisms can be pre-screened, and DNA from all of the positive clones can be pooled and used for making the biased combinatorial gene expression library"). Furthermore, Thompson et al. disclose various "normalization" procedures (e.g., see cited passages above, see also column 32, line 54; see also more generally section 5.1.6; see also column 17, lines 48-62; see especially claims 3, 21; see especially column 14, lines 50-51 wherein "slow growing" members were "equalized"; see also column 17, line 36 wherein DNA is "repaired" and thus their numbers are "equalized"; see also column 1, line 35 where "enzymes" are disclosed; see also column 4, line 32; see also column 9, line 14; see also column 10, line 2; see also column 34, line 35; see also column 6, line 55) to solve this "slow-growing" organism problem.

Thompson et al. further disclose **(c-d)** contacting a library containing clones of normalized polynucleotides from (b) with at least one oligonucleotide probe labeled with

a detectable molecule, wherein the probe comprises at least a portion of a polynucleotide sequence encoding an enzyme of interest (e.g., see Thompson et al., column 37, lines 30-36, "The combinatorial gene expression libraries of the invention may be pre-screened or screened by a variety of methods, including but not limited to ... hybridization to molecular beacon DNA probes (Tyagi et al.1996, *Nature Biotechnol*, 14:303-308) fluorescence activated cell sorting (FACS) and magnetic cell sorting (MACS)"; see also column 32, paragraph 1, "The preselected fragments of DNA contain genes encoding partial or complete biosynthetic pathways, and may be preselected by hybridizing to an initial DNA library a plurality of probes prepared from known genes that may be related to or are involved in producing compounds of interest"; see also column 9, line 14; see also column 33, line 35; see also column 34, line 45; see also column 4, paragraph 2 wherein various "enzymes" are disclosed including "esterases"; see also Thompson et al., see section 5.2.3, especially; section also section 5.2; see especially; see also column 32, lines 29-56; see also column 34, paragraphs 2-4; see especially column 34, lines 44-47; see also section 5.2.2. disclosing the use of fluorescent probes; see also column 33, line 38; see also column 37, line 35).

Furthermore, Thompson et al. disclose **(e)** separating clones with an analyzer that detects the detectable molecule using probes (e.g., see Thompson et al., column 33, line 39 e.g., disclosing the use of "FACS" analysis; see also column 37, line 35; see also column 35, paragraph 2, column 36, paragraph 2; see more generally section 5.2.2.; see also column 47, paragraph 1-7).

Thompson et al. also disclose **(f)** contacting the separated clones with a reporter system that comprises a substrate for the enzyme of interest (e.g., see, column 32, paragraph 4, "... screens for each library are chosen after comprehensive characterization of the host organism and, whenever possible, of the donor organisms. Assays in which the host organisms are positive are disqualified, while assays in which the donor organisms are positive are considered acceptable library ... screens. Substrates [which are used in the assay] are preferably the targets of enzymes relevant to desirable biosynthetic capabilities"; see also column 35, last paragraph, "The probe can be an enzyme substrate linked to a fluorogenic agent"; see also section 5.4.8.).

Finally, Thompson et al. disclose **(g)** identifying clones capable of modulating expression r activity of the reporter system thereby identifying a polynucleotide that encodes the enzyme of interest (e.g., see Thompson et al., column 5, paragraph 3, "While standard methods of screening gene expression libraries can be used, the libraries can be further modified to incorporate a reporter regimen tailored to identify clones that are expressing the desirable pathways and metabolic products [i.e., polynucleotides encoding the activity of interest]"; see also column 5, lines 55-65; see also abstract; see also figures 7-8, see also column 11, line 33-40; see also Thompson et al., section 5.2.1.; especially column 35, lines 38-67 disclosing reporter constructs with inducible promoters; see also claims 17, 33; see also column 34, line 35; see also column 35, line 66).

For ***claim 3***, Thompson et al. disclose an expression library (e.g., see Thompson et al., column 6, paragraph 4; see also column 5, paragraph 4, "standard methods of

screening gene expression libraries can be used"; see also figures 1-2; see also column 9, paragraph 4).

For ***claim 4***, Thompson et al. disclose a fluorescent molecule (see Thompson et al., column 35, paragraph 2; see also column 36, paragraph 2; see section 5.2.2., especially column 36, last two paragraphs, "A physiological probe as used herein is a fluorescent or colorigenic agent"; see also column 37, paragraphs 1-2).

For ***claim 5***, Thompson et al. disclose FACS (see Thompson et al., column 7, line 2; see also figure 9; see also column 33, line 39; see also column 35, line 10).

For ***claim 6***, Thompson et al. disclose a mixed population of organisms from an environmental sample (see Thompson et al., column 12, section 5.1.1. Donor Organisms, especially line 43, "Any organism can be a donor organism ... obtained from ... environmental samples").

For ***claim 7***, Thompson et al. disclose microorganisms (e.g., see Thompson et al., see column 12, line 59, "the invention is not limited to microorganism donors).

For ***claims 8-9***, Thompson et al. disclose extremophiles including thermophiles, acidophiles and halophiles (e.g., see Thompson et al., column 13, last paragraph; see especially column 14, line 2, "The donor organisms may be thermophilic, halophilic, acidophilic, barophilic, methanogenic").

For ***claim 10***, Thompson et al. teach reporter systems that are bioactive substrates (see Thompson et al., column 34, paragraphs 3-4, especially line 45; see especially column 36, last paragraph, "The probe can be an enzyme substrate"; see also column 47, line 28).

For ***claims 16-17***, Thompson et al. disclose encapsulation via a gel microdrop (e.g., see Thompson et al., column 38, line 15; see also column 38, line 38; see also column 37, line 57).

For ***claim 19***, Thompson et al. disclose any enzyme and provide several examples including esterase (e.g., see Thompson et al., column 9, line 14; see also column 33, line 35; see also column 34, line 45; see also column 4, paragraph 2).

For ***claim 20***, Thompson et al. disclose a detectable label (see Thompson et al., column 34, paragraphs 1-3; see also column 33, line 43).

For ***claim 22***, Thompson et al. disclose "small" molecules (see Thompson et al., column 30, paragraphs 6-8; see also column 4, paragraph 2).

For ***claim 23-25***, Thompson et al. disclose polynucleotides of interest comprise one or more operons (see Thompson et al., column 25, line 59; see especially column 26, last paragraph; see also column 36, paragraph 1; see most especially claim 9, "The gene expression library of claim 7 in which the cDNA or genomic DNA fragments comprise one or more operons, or portions thereof"). Thompson et al. also disclose operons for the polyketide syntheses (see Thompson et al., column 4, paragraph 2; see also column 13, paragraph 4, see also column 32, paragraph 3; see also column 60, paragraph 2; see also column 60, second to lat paragraph). Thompson et al. also disclose complete or incomplete metabolic pathways (see Thompson et al., column 32, paragraph 1, "The preselected fragments of DNA contain genes encoding partial or complete biosynthetic pathways, and may be preselected by hybridizing to an initial DNA library a plurality of probes prepared from known genes that may be related to or are involved in producing

compounds of interest"; see also column 6, line 47 providing definition of metabolic pathway; see also figure 1).

Response

6. Applicant's arguments directed to the above 35 U.S.C. § 102(e) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Thompson is silent regarding 'normalizing' environmental DNA to allow equal representation of polypeptides from all species present in a library assembled from a sample including a mixed population of organisms ... Applicants disagree with the assertion in the office action stating that Thompson discloses 'normalizing the plurality of polynucleotides'" and direct the Examiner's attention to various passages in the Thompson et al. in support of this position (e.g., see 11/1/04 Response, pages 11-12).

[2] Applicants argue, "Thompson does not use the term 'equalize' in connection with such activities ... Applicants disagree that such techniques would result in 'increasing the representation of rare species in the sample' ... [because] Thompson does not disclose that only rare polynucleotides would be need to be repaired or would be slow growing. For example, over-represented species are just as likely to have damages DNA as underrepresented species" (e.g., see 11/1/04 Response, page 12, paragraph 2).

[3] Applicants argue, Thompson uses the activity probe concept for pre-screening, pre-selecting and preparing "chimeric" and "biased" combinatorial expression libraries ... prior to screening" (e.g., see 11/1/04 Response, pages 12-13).

[4] Applicants argue, "... the dictionary definition of 'normalization' applied by the Examiner as 'to cause to conform to a norm or standard' is improperly applied ... because 'normalization' in the contexts of the present claims is 'a term of art'" and cite U.S. Patent 6,174, 673 in support of this position (e.g., see 11/1/04 Response, pages 13-14). In addition, Applicants also cite Soares et al. and Sambrook et al (e.g., see 11/1/04 Response, page 14, paragraph 2, see also Exhibit A and B).

[5] Applicants argue, "... the claim language prescribes normalization of the polynucleotides prior to formation of the library" (e.g., see 11/1/04 Response, page 14, paragraphs 3-4).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. Thompson et al. clearly discloses the process of "normalization" as outlined in the newly amended rejection above (e.g., see claim 1, part (b)). In addition, Applicant's arguments with regard to their "disagreement" fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Here, Applicants merely recite various passages in Thompson et al. without providing any rationale or reasoning how these passages support their argument (e.g., see 11/1/04 Response, page 12, paragraph 1, Thompson states ... Thompson goes

further to state ... Further Thompson states ... ." However, Applicants never state how these passages support their argument.

[2] The Examiner contends that "ipsis verbis" support is not the test and, as a result, Thompson et al. need not recite Applicants' exact phraseology (e.g., "[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968)). In addition, the Examiner notes that Applicants' contention that Thompson et al. would not 'increase the representation of rare species in the sample' is wholly unsupported and explicitly contradicted by the Thompson et al. reference (e.g., see Thompson et al., column 14, lines 46-60, "Since it is unlikely that all donor organisms in an environmental sample may be propagated at the same rate, if at all under laboratory conditions, some of the donor organisms may overgrow [i.e., abundant species] and lead to the loss or dilution of slow-growing organisms [i.e., rare species]. Thus, it may be preferable to prepare nucleic acids directly from donor organisms in an environmental sample without prior culturing in the laboratory [i.e., to allow normalization or "equalization of the slow-growing organisms]"). Finally, the Examiner notes that Applicants' arguments are not commensurate in scope with the claims. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "increasing representation of rare species in the sample") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

[3] The Examiner respectfully disagrees. MPEP § 2123 states, "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989)"). Here, Applicants have narrowly focused on only one "preferred embodiment" of Thompson et al. and thus have failed to appreciate "all" that the reference would teach in accordance with MPEP § 2123 and as outlined in the newly amended rejection above.

[4] The Examiner contends that words of a claim must be given their "plain meaning" unless they are clearly defined in the specification (e.g., see MPEP § 2111.01). Here, "normalization" is not defined in Applicants' specification. In addition, the Courts have upheld the use of "dictionary definitions" to determine the plain meaning of a claimed term (e.g., see *Ferguson Beauregard /Logic Controls v. Mega Systems*, 350 F.3d 1327, 1338, 69 USPQ2d 1001, 1009 (Fed. Cir. 2003)) (Dictionary definitions were used to determine the ordinary and customary meaning of the words "normal" and "predetermine" to those skilled in the art.). Thus, the Examiner's use of a dictionary is not "improper" as purported by Applicants.

In addition, the Examiner notes that the 6,174,673 Patent (referred to below as '673) does not provide a definition for the term "normalization" either. For example, in *Unitherm Food Systems Inc. v. Swift-Eckrich Inc.* the Court held that examples in a specification that are merely "illustrative" in nature do not provide an adequate definition for the alleged term of art because these examples do not exhaustively delineate and/or define the metes and bounds of the claim (e.g., see *Unitherm Food Systems Inc. v. Swift-Eckrich Inc.*, 71 USPQ2d 1705 (CA FC 2004)) (wherein the Court held that the term "golden brown" as it relates to the color of cooked meat

products should be given the broader "dictionary definition" because the "five illustrative examples" in the specification were merely "exemplary" in nature and did not exhaustively delineate the scope of the term). Here, the '673 patent merely recites an "illustrative" example drawn to "one embodiment" of the invention (e.g., see 11/1/04 Response, page 13, cited paragraph of '673 at bottom of page, "One embodiment for forming a normalized library ...") and thus does not provide and adequate definition for the term in accordance with *Unitherm Food Systems Inc. v. Swift-Eckrich Inc.* as set forth above.

Finally, the Examiner notes that Soares et al. and Sambrook et al. are not persuasive because Applicants have not distinctly and specifically pointed to any portions of either reference that would support their arguments.

[5] The Examiner contends that Thompson et al. disclose a normalization step "prior to" the formation of the library (see below) and notes that the slow growing-organisms could not be accommodated if they didn't i.e., Thompson et al. provides both an explicit and implicit teaching for this element (e.g., see Thompson et al., column 14, lines 46-60, "Since it is unlikely that all donor organisms in an environmental sample may be propagated at the same rate, if at all under laboratory conditions, some of the donor organisms may overgrow and lead to the loss or dilution of slow-growing organisms. Thus, it may be preferable to prepare nucleic acids directly from donor organisms in an environmental sample without prior culturing in the laboratory"; see also column 32, lines 14-16, "all the positive clones can be pooled and used for making the biased [i.e., normalized] combinatorial gene expression library. The initial library [i.e., the library prepared directly from donor organisms mentioned above "prior to" the formation of the

"normalized" library] may be amplified ... for making the biased [i.e., normalized] combinatorial gene expression library").

Accordingly, the 35 U.S.C. § 102(e) rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

7. Claims 1, 3-12, 16, 17, 19, 20 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson et al. (US Patent No. 5,824,485) (Filed **April 24, 1996**) and Miao et al. (Miao, F.; Todd, P.; Kompala, D. S. "A single-cell assay of β-galactosidase in recombinant *E. coli* using flow cytometry" Biotechnology and Bioengineering (**1993**), 42, 708-715).

For ***claims 1, 3-10, 16, 17, 19, 20 and 22-25***, Thompson et al. teach all the limitations stated in the 35 U.S.C. 102(e) rejection above (incorporated in its entirety herein by reference), which anticipates and, consequently, also renders obvious claims 1, 3-10, 16, 17, 19, 20 and 22-25.

The prior art teaching of Thompson et al. differs from the claimed invention as follows:

For ***claims 11-12***, the prior art teachings of Thompson et al. differs from the claimed invention by not specifically reciting the use of "C12FDG". Thompson et al. implies that C12FDG may be used by reciting the use of β-galactosidase in the reporter system that uses C12FDG i.e., C12FDG is commonly hydrolyzed by β-galactosidase (see Miao below), but the reference does not explicitly state that C12FDG is used.

However, Miao et al. teach the following limitations that are deficient in Thompson et al.:

For ***claims 11-12***, Miao et al. (see entire document) explicitly teach the use of "C12FDG" with a "lipophilic group" in assays using β-galactosidase like the one employed by Thompson et al. (see Miao et al., abstract; see also page 708, column 2, paragraph 1).

It would have been obvious to one skilled in the art at the time the invention was to use the C12FDG as taught by Miao et al. with the β-galactosidase enzyme reporter system as taught by Thompson et al. because Miao et al. explicitly states that the C12FDG substrate is specifically designed to be used in these types of assays with β-galactosidase. one would have been motivated to use the C12FDG because Miao et al. explicitly states that the C12FDG contains a lipophilic group that allows the substrate to penetrate through the cell membrane, which would be advantageous because according to Miao et al., "This improvement provides a great increase in intracellular fluorescence intensity and a reduction in dye transfer among cells. By using this new substrate, it becomes possible to separately count β-galactosidase-positive (plasmid-bearing) and B-galactosidase-negative (plasmid-free) bacterial cells using flow cytometry" (see Miao et al., page 708, column 2, paragraph 1). One of skill in the art would have been reasonably assured of success because Miao et al. shows a successful example using flow cytometry.

Response

8. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed

persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "The discussion above regarding the deficiencies of Thompson apply equally and are incorporated here" (e.g., see 11/1/04 Response, page 16, last paragraph).

[2] Applicants argue that Miao's disclosure fails to remedy the deficiencies in the Thompson et al. reference because Miao's disclose does not disclose a "normalized" library either (e.g., see 11/1/04 Response, page 17, paragraph 1). Applicants also state that there would be no "reasonable expectation of success" because neither reference teaches the "normalization" process (e.g., see 11/1/04 Response, page 17, paragraph 2).

This is not found persuasive for the following reasons:

[1] To the extent that Applicants are merely repeating their arguments to the Thompson et al. rejection under 35 U.S.C. § 102, the Examiner contends that those arguments have been adequately addressed in that section (see above), which are incorporated in their entirety herein by reference. Furthermore, in response to applicant's arguments against the Thompson et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[2] The Examiner contends that Thompson et al. disclose a successful "normalized" library (e.g., see newly amended rejection above; see also response to 35 U.S.C. § 102 rejection) and, as a result, Applicants' arguments are moot.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 3-12, 16, 17, 19, 20 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

A. Claim 1 was amended to recite, "... normalizing the plurality of polynucleotides to allow equal representation of all polynucleotides in the mixed population." However, the Examiner contends that the specification does not provide support for "equal" representation. Specifically, the Examiner can only find support for "more equal" representation (e.g., see specification, page 20, lines 25-27, "Additionally, a normalization of the environmental DNA present in these samples could allow more equal representation of the DNA from all of the species present in the original sample"), which by definition would be something less than "exactly equal" representation. If applicant believes this rejection is in error, applicant must disclose where in the

specification support for this amendment can be found in accordance with MPEP 714.02.

Therefore, claim 1 and all dependent claims are rejected as New Matter.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
January 30, 2005